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EXAMINER	
DUNSTON, JENNIFER ANN	

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/091,177	COME ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/3/2005, 10/17/2005 and 7/20/2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-66* is/are pending in the application.

4a) Of the above claim(s) *1-27,32, 43-45, 47,56-62 and 65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-31,33-42,46,48-55 and 63* is/are rejected.

7)☒ Claim(s) *64 and 66* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 March 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/05,4/23/03,4/28/03*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 10/3/2005, in which claims 1, 12, 18, 24, 25 and 48 were amended. Currently, claims 1-66 are pending in the instant application.

Correction of Inventorship Under 37 CFR 1.48(a)

In view of the papers filed 10/17/2003, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed by the addition of Christoph Reichel as an inventor.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Election/Restrictions

Applicant's election with traverse of Group IV in the reply filed on 7/20/2005 is acknowledged. The traversal is on the ground(s) that all pending claims can be examined without imposing additional serious search burden on the Examiner due to the shared common features that facilitate searching. This is not found persuasive because the search of the products will require an extensive search of the patent and non-patent literature to identify the claimed structural features. Each claimed structure will require a separate search of the patent and non-patent literature. Furthermore, a reference that teaches a claimed structure will not necessarily

teach the claimed method. Moreover, each method will require a separate search of the patent and non-patent literature to identify the method steps not shared with any other group. Therefore, the search of Group IV is not coextensive with the search for any other group. The additional searching required to search any additional groups would impose a serious search burden.

Applicant's election with traverse of the following species in the reply filed on 7/20/2005 is acknowledged: "methotrexate or a derivative thereof" for R1, X represents O and n=5 for Y, and "identifying a positive ligand binding cell in which an increase in the level of transcription of the reporter gene has occurred for the method step of detecting (see pages 21-22 of the response filed 7/20/2005). The traversal is on the ground(s) that the basis for a species election for the method step must be clarified. The response asserts that the Examiner has attempted to divide steps (iii) and (iv) of claim 28 (see page 22 of the response). This is not found persuasive because at least two different methods of detecting are claimed. For example, claim 28 requires the detection of a positive ligand-binding cell by an increase in the level of transcription of a reporter gene, whereas claim 43 requires the detection of a ligand binding by detecting the degree of cleavage by a ubiquitin-specified protease of the first ligand-binding polypeptide between Cub and Z. These two method steps are distinct and do not render the other obvious. Further, the response asserts that a species election was not required in the continuation-in-part application 10/234985, which was examined by a different Examiner (see page 23 of the response). This is not found persuasive because the requirement for restriction is at the discretion of the Examiner (MPEP § 803).

Applicant's election with traverse, in the reply filed on 10/3/2005, of the second to last compound in Table 2 as the elected species for R2 is acknowledged. The traversal is on the ground(s) that a search using R1 as methotrexate or derivatives thereof already provides a sufficient focus for a clear search, and no additional search burden will result from withdrawing the species election. With regard to searching the structure of the hybrid ligand in the context of the claimed assay, this is found persuasive. The species election for Y and R2 has been WITHDRAWN. The species election for R1 and the method step of detecting are maintained. Currently, claim 46 is generic to both species types (R1 and the method step of detecting).

The requirement is still deemed proper and is therefore made FINAL.

Applicant has indicated that claims 28-46, 48-56, 63, 64 and 66 read on the elected invention. However, claims 43-45 do not read on the elected method step for identifying a detectable event. Claim 32 does not read on the elected R1 (methotrexate) in that methotrexate is a competitive inhibitor of dihydrofolate reductase and does not form a covalent bond with its binding partner (P1). Therefore, claims 28-31, 33-42, 46, 48-55, 63, 64 and 66 read on the elected invention.

Claims 1-27, 47, 56-62 and 65 are withdrawn from consideration as being drawn to a non-elected invention. Claims 32 and 43-45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the replies filed on 7/20/2005 and 10/3/2005.

An examination on the merits of claims 28-31, 33-42, 46, 48-55, 63, 64 and 66 follows.

Information Disclosure Statement

Receipt of information disclosure statements, filed on 4/23/2003, 4/28/2003 and 7/20/2005, is acknowledged. The signed and initialed PTO 1449s have been mailed with this action.

Drawings

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: the individual panels of Figures 1, 4, 6, 7 and 16 are not separately described in the "Brief Description of the Figures" section of the specification. Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

Claim 66 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 66 depends from claim 63, which recites, "using a method of claim 28, 38, 43 or 44." Claim 66 does not recite the use of the method of claim 47. Thus, claim 66 broadens the scope of claim 63.

Claims 64 and 66 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

In the instant case, claim 64 refers to claim 63 in the preamble and claims "28, 38, 43 or 44" in the body of the claim. These two references are not in the alternative. Claim 66 refers to claim 63 and claim 47; however, the references are not in the alternative.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 38-42 and 48-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 38 is vague and indefinite in that the claim recites, "wherein R1 binds to or inhibits a kinase" and thus limits R1 to a kinase inhibitor. However, applicants have elected

methotrexate for R1 and have indicated that claim 38 reads on the elected species for R1. In fact, claim 42 limits R1 to a structure selected from the Markush-type group presented in the claim, which lists methotrexate as a structure capable of functioning as R1. However, The Online Medical Dictionary defines "methotrexate" as an analog of dihydrofolate. Further, the dictionary indicates that methotrexate inhibits dihydrofolate reductase and kills rapidly growing cells. However, the dictionary definition does not indicate that methotrexate is a kinase inhibitor. The specification does not define methotrexate as a kinase inhibitor. Based upon the teachings of the specification, it appears as though R2 is intended to be a kinase inhibitor (e.g. page 76, last paragraph; Example 2), such as a kinase inhibitor selected from Table 2 (e.g. claims 39 and 40). Therefore, the metes and bounds of the structural and functional characteristics of the hybrid ligand used in the method of claim 38 are unclear.

Claims 39-42 depend from claim 38, and thus are indefinite for the same reasons as applied to claim 38.

Claim 42 is vague and indefinite in that the metes and bounds of the term "derivative thereof" are unclear. The term is unclear in that the term is not clearly defined in the instant specification. A "derivative" would represent a molecule resulting from an undefined series of transformations, with any changes being potentially encompassed, such that essentially any molecule might result, given all the necessary transformation steps. As such, the scope of the claims is not clearly defined, as possibly any molecule might be encompassed.

Claim 42 is vague and indefinite in that the metes and bounds of the phrase "minor structural modifications" are unclear. The phrase is unclear in that it is not clearly defined in the instant specification. The term "minor" is a relative term. Given the absence of a clear

definition, the metes and bounds of the phrase are subjective and may vary depending upon one's opinion of the degree to which a modification is a minor modification.

Claim 48 is vague and indefinite in that the metes and bounds of the phrase "minor structural modifications" are unclear. The phrase is unclear in that it is not clearly defined in the instant specification. The term "minor" is a relative term. Given the absence of a clear definition, the metes and bounds of the phrase are subjective and may vary depending upon one's opinion of the degree to which a modification is a minor modification.

Claim 49 depends from claim 48, and thus is indefinite for the same reasons as applied to claim 48.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention and breadth of the claims: The claims are drawn to a method of identifying polypeptide sequences that bind to a user-specified ligand, wherein the ligand has the general formula R1-Y-R2 and R1 binds to or inhibits a kinase. Applicants have elected methotrexate and derivatives thereof with minor structural modifications for R1 and have indicated that claim 38 reads on the elected species for R1. Claim 42 limits R1 to a structure selected from the Markush-type group presented in the claim, which lists methotrexate as a structure capable of functioning as R1. The nature of the invention is complex in that methotrexate must function as a kinase inhibitor to meet the functional limitations set forth by claim 38.

The claims are broad in that they encompass unlimited structural modifications to the methotrexate structure.

Guidance of the specification and existence of working examples: The specification does not define methotrexate as a kinase inhibitor. Based upon the teachings of the specification, it appears as though R2 is intended to be a kinase inhibitor (e.g. page 76, last paragraph; Example 2), such as a kinase inhibitor selected from Table 2 (e.g. claims 39 and 40).

Predictability and state of the art: The prior art teaches that methotrexate binds very tightly to dihydrofolate reductase (Matthews et al. Science, Vol. 197, No. 4302, pages 452-455, 1977; e.g. page 453, paragraph bridging center and right columns; Figure 1). Dihydrofolate reductase catalyzes an oxidation-reduction reaction and does not catalyze the phosphorylation-dephoshporylation of proteins (ExPasy Entry for EC 1.5.1.3). Thus, methotrexate is not a kinase inhibitor.

Amount of experimentation necessary: The quantity of experimentation is high, as the skilled artisan would have to envision numerous structural modifications of methotrexate, synthesize the compounds, and test the compounds for the ability to inhibit a kinase. Given the number of structural changes encompassed by the claims and the large number of kinases that could be tested, one would be required to conduct a large amount of trial and error experimentation. This would require a large amount of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 38-42 are not considered to be enabled by the instant specification.

Claims 28-31, 33-42, 46, 48-55 and 63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to or encompass a set of compounds and derivatives thereof with "minor" structural modifications. Applicants have elected methotrexate and derivatives thereof with minor structural modifications as the compound represented by R1 of the hybrid ligand R1-Y-R2, which is used in the claimed methods. Thus, the rejected claims encompass the step of

providing a genus of hybrid ligands where R1 is methotrexate or a derivative thereof, where the hybrid ligand is capable of binding to a fusion protein comprising a binding domain capable of binding R1.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification describes the structure of methotrexate in the context of the hybrid ligands used in the claimed method (e.g. hybrid ligand GPC 285985). No description is provided of any alteration of the structure, which retains the binding capacity with respect to its ligand. No description is provided in either the specification or the prior art which provides a structure-function relationship to allow one of skill in the art to determine *a priori* those variant molecules that retain a useful function in the invention. The prior art teaches that, while it may be desirable to modify the structure of a compound used in a hybrid ligand, modifications could interfere with the binding of the compound to the ligand (e.g. Spencer et al (Science, Vol. 262, No. 5136, pages 1019-1024, 1993; e.g. page 1020, left column, 1st full paragraph).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed

chemical structure of the encompassed genus of promoter elements, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or identification. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Given the very large genus of compounds encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to the necessary structure required for function in the claimed method, the skilled artisan would not have been able to envision a sufficient number of specific embodiments that meet the functional limitations of the claims to describe the broadly claimed genus. Thus, there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those modified compounds that satisfy the functional limitations of the claims. Therefore, the skilled artisan would have reasonably concluded applicants were not in possession of the claimed invention for claims 28-31, 33-42, 46, 48-55 and 63.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 38, 42, 52-53 and 63 are rejected under 35 U.S.C. 102(a) as being anticipated by Lin et al (Journal of the American Chemical Society, Vol. 122, pages 4247-4248 and S1-S12, April 13, 2000; see the entire reference).

The claims encompass the step of providing a hybrid ligand of the general formula R1-Y-R2. Applicant has elected methotrexate as R1. For the purposes of this art rejection, the claims have been interpreted such that methotrexate meets the structural and functional limitations of the claimed method with regard to the ability of the structure to function as a kinase inhibitor.

Lin et al teach a method of identifying a polypeptide sequence that binds to a user-specified ligand, comprising the steps of (i) providing a hybrid ligand comprising methotrexate linked to dexamethasone through a linker region, (ii) introducing the hybrid ligand into yeast cells comprising a LacZ reporter gene operably linked to a LexA binding site, a first chimeric gene encoding a fusion polypeptide of LexA and DHFR, a second chimeric gene encoding a fusion protein of GR and B42, (iii) allowing the hybrid ligand to bind the first and second fusion proteins to result in an increase in the level of the transcription of the reporter gene, (iv) identifying a positive ligand binding cell by detecting blue colonies of yeast grown on X-gal containing plates, and (v) identifying the nucleic acid sequence of the second chimeric gene (e.g.

page 4248, left column; Figures 1 and 2; Scheme 1; page S6). Further, Lin et al teach the assay where one of the fusion proteins is deleted to detect the effect of the hybrid ligand independent of the formation of the trimeric complex of the two fusion proteins and the hybrid ligand (e.g. page 4248, left column, last paragraph). Moreover, Lin et al teach the assay in the absence of the hybrid ligand to confirm that the transcription of the reporter gene is dependent on the presence of the hybrid ligand and fusion proteins (e.g. Figure 2). The publication of the methods taught by Lin et al provides the public with access to the data, nucleic acids and polypeptides of the disclosed method.

Claims 28, 30-31, 33-34, 46, 52-53 and 63 are rejected under 35 U.S.C. 102(b) as being unpatentable over Keenan et al (Bioorg. Med. Chem. Vol. 6, pages 1309-1335, 1998; see the entire reference) as evidenced by Amara et al (PNAS, USA, Vol. 94, pages 10618-10623, 1997; see the entire reference) and Bierer et al (PNAS, USA, Vol. 87, pages 9231-9235, 1990; see the entire reference).

Regarding claims 28, 33-34 and 46, Keenan et al teach the method of identify binding of a polypeptide sequence to a user-specified ligand, comprising the steps of (i) providing a hybrid ligand such as dimerized FK1012 linked by polyehtylene linkers, (ii) introducing the hybrid ligand into a population of cells containing a SEAP reporter gene operably linked to ZFHD1 binding sequences, a first chimeric gene comprising encoding a fusion protein containing three FKBP binding domains and a DNA binding domain from ZFHD1, and a second chimeric gene encoding a fusion polypeptide containing three FKBP binding domains and a transcription activation domain from the NF-κB p65 subunit, and (iii) allowing the hybrid ligand to bind the

FKBP binding domains to induce dimerization such that transcription of the SEAP reporter gene is increased, and (iv) identifying positive ligand binding cells by activation of SEAP, and (v) identifying the nucleic acid sequence of the second chimeric gene (e.g. page 1334, Assay for inducible transcriptional activation; Figure 3; Table 1). Keenan et al teach that the method used to assay for inducible transcriptional activation was performed as previously described by Amara et al (e.g. page 10620, right column, 1st full paragraph; paragraph bridging pages 10618-10619; Figure 4). Keenan et al teach the use of hybrid ligands, wherein R1 and R2 are FK1012 and Y is of the formula $(CH2\text{-}O\text{-}CH2)_n$, where n=2, 3, 4 or 5, (e.g. Table 1, compounds AP1427, AP1592, AP1511, and AP1578).

Regarding claims 30-31, the hybrid ligands taught by Keenan et al bind to FKBP with a dissociation constant (K_D) of less than 1 μM. Keenan et al teach that the affinity of structure 2d is threefold better than the original model monomer 2a, and the prior art teaches that the dissociation constant of FK506 to FKBP is in the nanomolar range (e.g. Bierer et al, page 9231, paragraph bridging columns). Bierer et al is used here only to demonstrate that the dissociation constants of the ligands taught by Keenan are less than 1 μM.

Regarding claim 52, Keenan et al teach the addition of the hybrid ligand to cells in the absence of the fusion proteins (e.g. Table 1, Apoptosis; page 1334, Assay for inducible Fas activation in cell lines).

Regarding claim 53, Keenan et al teach the measurement of SEAP activity in mock transfected cells to identify background SEAP activity in the absence of the hybrid ligand (e.g. page 1334, Assay for inducible transcriptional activation).

Regarding claim 63, the publication of the methods taught by Keenan et al and the papers cited by Keenan et al provides the public with access to the data, nucleic acids and polypeptides of the disclosed method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 29 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keenan et al (Bioorg. Med. Chem. Vol. 6, pages 1309-1335, 1998; see the entire reference) in view of Licitra et al (PNAS, USA, Vol. 93, pages 12817-12821, 1996; see the entire reference) as evidenced by Amara et al (PNAS, USA, Vol. 94, pages 10618-10623, 1997; see the entire reference).

The teachings of Keenan et al are described above and applied as before.

Keenan et al do not teach hybrid ligands where R1 differs from R2 and do not teach the screening of a library of nucleic acid sequences. Further, Keenan et al do not teach the use of the LacZ reporter gene.

Licitra et al teach a yeast three-hybrid assay, wherein a hybrid ligand of Dexamethasone and FK506 is used to screen a cDNA library for proteins capable of binding to FK506 (e.g. page 12818, Three-Hybrid Screen for FK506-Binding Proteins; Figures 1-3). Licitra et al teach the identification of positive interactions using the LacZ reporter gene (e.g. Figure 3). Licitra et al teach that the yeast three-hybrid assay has advantages over classical methods for identifying receptors for small ligand in that the system allows the direct isolation and identification of cDNAs encoding receptors and the system easily allows one to manipulate a large number of yeast colonies to study the structure-function relationship of ligand receptor interaction (e.g. page 12820, right column, last full paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the hybrid ligand of Keenan et al to include the R1 and R2 substituents and screening of the cDNA library using the LacZ reporter gene as taught by Licitra et al because Keenan et al teach it is within the ordinary skill in the art to use polyethylene linkers to link FK506 derivatives and teach the identification of a nucleic acid sequence encoding an FKBP protein capable of binding to the FK506 derivative and both Keenan et al and Licitra et al teach the use of a hybrid ligand in a yeast three hybrid assay.

One would have been motivated to make such a modification in order to receive the expected benefit of being able to identify proteins capable of binding FK506 as taught by Licitra et al. Further, one would have been motivated to use the assay to manipulate the structure of the

ligand, as taught by Keenan et al, and test for binding to the identified interactors as taught by Licitra et al. Moreover, one would have been motivated to use the LacZ reporter gene to be able to easily visualize positive interaction by testing for blue color formation in the presence of X-gal as taught by Licitra et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 29, 35-36, 41 and 48-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keenan et al (Bioorg. Med. Chem. Vol. 6, pages 1309-1335, 1998; see the entire reference) in view of Licitra et al (PNAS, USA, Vol. 93, pages 12817-12821, 1996; see the entire reference) further in view of Lin et al (Journal of the American Chemical Society, Vol. 122, pages 4247-4248 and S1-S12, April 13, 2000; see the entire reference) as evidenced by Amara et al (PNAS, USA, Vol. 94, pages 10618-10623, 1997; see the entire reference).

The claims encompass the step of providing a hybrid ligand of the general formula R1-Y-R2. Applicant has elected methotrexate as R1. For the purposes of this art rejection, the claims have been interpreted such that methotrexate meets the structural and functional limitations of the claimed method with regard to the ability of the structure to function as a kinase inhibitor.

The teachings of Keenan et al are described above and applied as before.

Keenan et al do not teach hybrid ligands where R1 differs from R2 and do not teach the screening of a library of nucleic acid sequences. Further, Keenan et al do not teach the use of the LacZ reporter gene. Keenan et al do not teach the use of methotrexate as the R1 group in the hybrid ligand.

Licitra et al teach a yeast three-hybrid assay, wherein a hybrid ligand of dexamethasone and FK506 is used to screen a cDNA library for proteins capable of binding to FK506 (e.g. page 12818, Three-Hybrid Screen for FK506-Binding Proteins; Figures 1-3). Licitra et al teach the identification of positive interactions using the LacZ reporter gene (e.g. Figure 3). Licitra et al teach that the yeast three-hybrid assay has advantages over classical methods for identifying receptors for small ligand in that the system allows the direct isolation and identification of cDNAs encoding receptors and the system easily allows one to manipulate a large number of yeast colonies to study the structure-function relationship of ligand receptor interaction (e.g. page 12820, right column, last full paragraph).

Lin et al teach a method of identifying a polypeptide sequence that binds to a user-specified ligand, comprising the steps of (i) providing a hybrid ligand comprising methotrexate linked to dexamethasone through a linker region, (ii) introducing the hybrid ligand into yeast cells comprising a LacZ reporter gene operably linked to a LexA binding site, a first chimeric gene encoding a fusion polypeptide of LexA and DHFR, a second chimeric gene encoding a fusion protein of GR and B42, (iii) allowing the hybrid ligand to bind the first and second fusion proteins to result in an increase in the level of the transcription of the reporter gene, (iv) identifying a positive ligand binding cell by detecting blue colonies of yeast grown on X-gal containing plates, and (v) identifying the nucleic acid sequence of the second chimeric gene (e.g. page 4248, left column; Figures 1 and 2; Scheme 1; page S6). Further, Lin et al teach that methotrexate has a picomolar affinity for DHFR and can induce LacZ gene expression at levels 150-fold higher than a dexamethason-FK506 hybrid ligand (e.g. page 14247, right column, 1st paragraph; page 4248, right column, 1st paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the hybrid ligand of Keenan et al to include the R1 and R2 substituents and screening of the cDNA library using the LacZ reporter gene as taught by Licitra et al because Keenan et al teach it is within the ordinary skill in the art to use polyethylene linkers to link FK506 derivatives and teach the identification of a nucleic acid sequence encoding an FKBP protein capable of binding to the FK506 derivative and both Keenan et al and Licitra et al teach the use of a hybrid ligand in a yeast three hybrid assay. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the three hybrid assay of Keenan et al and Licitra et al to include methotrexate as the R1 group of the hybrid ligand because Licitra et al and Lin et al teach it is within the skill of the art to use hybrid ligands where R1 differs from R2.

One would have been motivated to make such a modification in order to receive the expected benefit of being able to identify proteins capable of binding FK506 as taught by Licitra et al. Further, one would have been motivated to use the assay to manipulate the structure of the ligand, as taught by Keenan et al, and test for binding to the identified interactors as taught by Licitra et al. One would have been motivated to use methotrexate as the R1 group in the hybrid ligand because Lin et al teach that methotrexate has picomolar affinity for DHFR and can induce higher levels of LacZ gene expression, and thus one could identify weaker interactions. Moreover, one would have been motivated to use the LacZ reporter gene to be able to easily visualize positive interaction by testing for blue color formation in the presence of X-gal as taught by Licitra et al and Lin et al. Based upon the teachings of the cited references, the high

skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 29, 35-36, 41 and 48-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keenan et al (Bioorg. Med. Chem. Vol. 6, pages 1309-1335, 1998; see the entire reference) in view of Licitra et al (PNAS, USA, Vol. 93, pages 12817-12821, 1996; see the entire reference) further in view of Lin et al (Journal of the American Chemical Society, Vol. 122, pages 4247-4248 and S1-S12, April 13, 2000; see the entire reference), Sota et al (Analytical Chemistry, Vol. 70, pages 2019-2024, 1998; see the entire reference) and Karlsson et al (US Patent No. 6,143,574; see the entire reference) as evidenced by Amara et al (PNAS, USA, Vol. 94, pages 10618-10623, 1997; see the entire reference).

The claims encompass the step of providing a hybrid ligand of the general formula R1-Y-R2. Applicant has elected methotrexate as R1. For the purposes of this art rejection, the claims have been interpreted such that methotrexate meets the structural and functional limitations of the claimed method with regard to the ability of the structure to function as a kinase inhibitor.

The teachings of Keenan et al are described above and applied as before.

Keenan et al do not teach hybrid ligands where R1 differs from R2 and do not teach the screening of a library of nucleic acid sequences. Further, Keenan et al do not teach the use of the LacZ reporter gene. Keenan et al do not teach the use of methotrexate as the R1 group in the hybrid ligand.

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12818, Three-Hybrid Screen for FK506-Binding Proteins; Figures 1-3). Licitra et al teach the identification of positive interactions using the LacZ reporter gene (e.g. Figure 3). Licitra et al teach that the yeast three-hybrid assay has advantages over classical methods for identifying receptors for small ligand in that the system allows the direct isolation and identification of cDNAs encoding receptors and the system easily allows one to manipulate a large number of yeast colonies to study the structure-function relationship of ligand receptor interaction (e.g. page 12820, right column, last full paragraph).

Lin et al teach a method of identifying a polypeptide sequence that binds to a user-specified ligand, comprising the steps of (i) providing a hybrid ligand comprising methotrexate linked to dexamethasone through a linker region, (ii) introducing the hybrid ligand into yeast cells comprising a LacZ reporter gene operably linked to a LexA binding site, a first chimeric gene encoding a fusion polypeptide of LexA and DHFR, a second chimeric gene encoding a fusion protein of GR and B42, (iii) allowing the hybrid ligand to bind the first and second fusion proteins to result in an increase in the level of the transcription of the reporter gene, (iv) identifying a positive ligand binding cell by detecting blue colonies of yeast grown on X-gal containing plates, and (v) identifying the nucleic acid sequence of the second chimeric gene (e.g. page 4248, left column; Figures 1 and 2; Scheme 1; page S6). Further, Lin et al teach that methotrexate has a picomolar affinity for DHFR and can induce LacZ gene expression at levels 150-fold higher than a dexamethason-FK506 hybrid ligand (e.g. page 14247, right column, 1st paragraph; page 4248, right column, 1st paragraph).

Karlsson et al teach that the BIAcore instrument uses the phenomenon of surface plasmon resonance to study the binding of analytes to receptors immobilized on a sensor chip to

allow the affinity and kinetic analysis of interactions between soluble analytes and their immobilized binding partners to be determined (e.g. column 1, lines 11-45). Karlsson et al teach that affinity and kinetic properties for the solution interaction between an analyte and a binding partner can be determined by the following steps: (i) mixing the analyte with an immobilized binding partner (e.g. column 2, lines 3-15; column 3, lines 17-20).

Sota et al teach a surface plasmon resonance chip with dihydrofolate reductase immobilized on the surface of the chip (e.g. page 2020, paragraph bridging columns). Further, Sota et al teach it is within the skill of the art to use surface plasmon resonance to monitor the binding of solute molecules to the immobilized protein (e.g. paragraph bridging pages 2019-2020).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the hybrid ligand of Keenan et al to include the R1 and R2 substituents and screening of the cDNA library using the LacZ reporter gene as taught by Licitra et al because Keenan et al teach it is within the ordinary skill in the art to use polyethylene linkers to link FK506 derivatives and teach the identification of a nucleic acid sequence encoding an FKBP protein capable of binding to the FK506 derivative and both Keenan et al and Licitra et al teach the use of a hybrid ligand in a yeast three hybrid assay. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the three hybrid assay of Keenan et al and Licitra et al to include methotrexate as the R1 group of the hybrid ligand because Licitra et al and Lin et al teach it is within the skill of the art to use hybrid ligands where R1 differs from R2. Moreover, it would have been obvious to one of ordinary skill in the art to use surface plasmon resonance to determine the dissociation constant of the hybrid ligand

of the combined teachings of Keenan et al, Licitra et al and Lin et al because Karlsson et al and Sota et al teach it is within the skill of the art to determine dissociation constants. Further, Lin et al teach the determination of the dissociation constant of the methotrexate-dexamethasone hybrid ligand and comparison of the methotrexate-dexamethasone hybrid ligand to the dexamethasone-FK506 hybrid ligand in a LacZ transcription assay, which complements the studies of Keenan et al where the transcriptional activation of hybrid ligands containing different linkers was tested by transcriptional activation of a reporter gene. Thus, one of skill in the art would have recognized the importance of determining the dissociation constant of the hybrid ligand and binding protein as a measure of the sensitivity of the assay.

One would have been motivated to make such a modification in order to receive the expected benefit of being able to identify proteins capable of binding FK506 as taught by Licitra et al. Further, one would have been motivated to use the assay to manipulate the structure of the ligand, as taught by Keenan et al, and test for binding to the identified interactors as taught by Licitra et al. One would have been motivated to use methotrexate as the R1 group in the hybrid ligand because Lin et al teach that methotrexate has picomolar affinity for DHFR and can induce higher levels of LacZ gene expression, and thus one could identify weaker interactions. Furthermore, one would have been motivated to determine the dissociation constants of hybrid ligands containing methotrexate and the different linkers taught by Keenan et al to identify the hybrid molecules with the lowest dissociation constants to optimize the sensitivity of the assay. Moreover, one would have been motivated to use the LacZ reporter gene to be able to easily visualize positive interaction by testing for blue color formation in the presence of X-gal as taught by Licitra et al and Lin et al. Based upon the teachings of the cited references, the high

skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 54-55 are rejected under 35 U.S.C. 102(a) as being anticipated by Lin et al (Journal of the American Chemical Society, Vol. 122, pages 4247-4248 and S1-S12, April 13, 2000; see the entire reference) in view of Mehta (WO 00/07018; see the entire reference).

The claims encompass the step of providing a hybrid ligand of the general formula R1-Y-R2. Applicant has elected methotrexate as R1. For the purposes of this art rejection, the claims have been interpreted such that methotrexate meets the structural and functional limitations of the claimed method with regard to the ability of the structure to function as a kinase inhibitor.

The teachings of Lin et al are described above and applied as before.

Lin et al do not teach the use of a microtiter plate to confirm that the transcription of the reporter gene is dependent on the presence of the hybrid ligand.

Mehta et al teach the confirmation of the dependence of yeast three hybrid ligand interactions on the presence of both fusion proteins and the hybrid ligand by placing yeast cells in a well of a 96 well plate with hybrid ligand only or no hybrid molecule to serve as controls in the assay (e.g. Example 4). Further, Mehta et al teach the screening of libraries to identify numerous proteins that may interact with the hybrid ligand and teach the confirmation of the interactions using the 96-well microtiter assay (e.g. Example 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the yeast three hybrid assay of Lin et al to include the use of the mcirotiter plate as taught by Mehta et al because both Lin et al and Mehta et al teach it is within the

ordinary skill in the art to use hybrid ligands in a yeast three hybrid assay. Further, it would have been obvious to conduct the assay on greater than 10 ligand-binding cell types because the assay can result in the identification of at least 10 ligand-binding cell types or can be repeated at least 10 times to identify 10 ligand-binding cell types.

One would have been motivated to make such a modification in order to receive the expected benefit of being able to use fewer reagents and to be able to perform more assays in less space by using the microtiter plate as taught by Mehta et al. Further, one would have been motivated to conduct the assay on at least 10 ligand-binding cell types in order to confirm each interaction identified in the screen. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 54-55 is rejected under 35 U.S.C. 102(a) as being anticipated by Keenan et al (Bioorg. Med. Chem. Vol. 6, pages 1309-1335, 1998; see the entire reference) as evidenced by Amara et al (PNAS, USA, Vol. 94, pages 10618-10623, 1997; see the entire reference) in view of Mehta (WO 00/07018; see the entire reference).

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One would have been motivated to make such a modification in order to receive the expected benefit of being able to use fewer reagents and to be able to perform more assays in less space by using the microtiter plate as taught by Mehta et al. Further, one would have been motivated to conduct the assay on at least 10 ligand-binding cell types in order to confirm each interaction identified in the screen. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached at 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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